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Electronic Measurement of Compliance With Mercaptopurine in Pediatric Patients With Acute Lymphoblastic Leukemia

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Twenty-four pediatric patients with acute lymphoblastic leukemia (ALL) on maintenance therapy were evaluated for their compliance with taking their prescribed doses of oral mercaptopurine (6-MP).

Procedure and Results. We utilized the Medication Event Monitoring System (MEMS; Aprex Corporation, Fremont, CA) for the study. Compliance was defined as the number of days doses were taken as a percentage of the total number of days doses were prescribed during the study period. The mean age of the patients was 7.3 years (range 2.6–17.2 (years). Patients were evaluated for a mean of 44 days (range 15–94 days). Thirty-three percent of patients (8) took less than 90% and 17% (4) took less than 80% of their prescribed pills. Eight patients were also evaluated for a difference in compliance between morning and evening administration. For the comparison of compliance between a morning vs. an evening schedule a trend toward improved compliance in the evening was found. Five patients had an increase and one patient a decrease in compliance with an evening schedule (differences ranged from 0.2% to 51.3%), with two patients having 100% compliance on both schedules.

Conclusions. Our data raise concern that a significant proportion of pediatric patients are non-compliant with pill taking and demonstrate that the timing of administration of 6-MP in children with ALL may be crucial in some patients and supports the hypothesis that evening administration of 6-MP is associated with a lower risk of relapse. Med. Pediatr. Oncol. 30: 85–90, 1998.

Key words: Medication Event Monitoring System; compliance; pediatric ALL patients; 6-mercaptopurine

INTRODUCTION

Leukemias are the most common form of pediatric malignancies, accounting for one third of the cases of childhood cancer. Acute lymphoblastic leukemia (ALL) accounts for about 75% of cases of childhood leukemia [1]. With present therapy nearly 95% of children with this disease attain a complete remission and greater than half remain in continuous remission for more than 5 years [2]. Unfortunately, a substantial number of children still experience relapse in either bone marrow or extramedullary sites. Elucidating the factors which play a role in recurrence of disease is crucial in improving the treatment of ALL.

Current management of ALL in the pediatric population comprises several phases of therapy, usually including induction therapy, consolidation, and a period of maintenance chemotherapy continuing for a total duration of up to 3 years. Depending on the assignment of risk factors, the intensity of therapy can vary, as can the types and dosages of drugs used in different treatment protocols. Oral mercaptopurine (6-MP) and methotrexate are important components of many ALL protocols.

6-MP is a purine analog with antineoplastic and immunosuppressive activity. The extent of systemic exposure to this agent for any given dosage may vary from individual to individual due to large interpatient variability in drug handling. The importance of the level of systemic exposure to 6-MP has been emphasized by previous work which demonstrated that low systemic exposure, as reflected by area under the concentration vs. time curve, during maintenance therapy for ALL in childhood adversely affects the prognosis [3]. Several studies have related outcome to variables of 6-MP therapy. Factors including low plasma levels [4], morning administration [5], and high levels of thiopurine methyltransferase [6] have all been implicated in poor outcomes.

Compliance with medication regimens can be problematic for some patients. The assumption that the threat

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TABLE I. Patient Characteristics

No. of patients (n)	24
Males/females	15/9
Age (years)	7.3 ± 4.6[a] (2.6–17.2)[b]
Time from diagnosis (months)	19.6 ± 10.4 (2.0–33.8)
Duration on maintenance therapy (months)	12.4 ± 10.2 (0–30.9)
No. of days monitored per patient	44 ± 20.2 (15–94)

[a]Mean ± standard deviation (SD).
[b]Range.

of cancer and the fear of a fatal outcome will insure adherence to treatment is not always valid as studies have demonstrated non-compliance in cancer patients [7,8]. As oral 6-MP is an important component of treatment protocols for ALL we undertook an evaluation of compliance with oral 6-MP in a cohort of pediatric patients utilizing electronic monitoring. To the best of our knowledge, there is no similar study in childhood ALL. In particular, we wish to introduce physicians treating such patients to the clinical advantages of novel electronic measurement of compliance in children.

PATIENTS AND METHODS

Patients

Twenty-four pediatric patients with ALL in remission followed in the hematology/oncology outpatient clinic at the Hospital for Sick Children were evaluated. All were in the maintenance phase of their treatment protocols. Maintenance therapy consisted of monthly administration of doses of vincristine and prednisone, administration of weekly oral or biweekly intravenous doses of methotrexate, daily oral doses of 6-MP, and intrathecal methotrexate every 3 months. Total duration of treatment including maintenance is 3 years on our treatment protocols. The characteristics of our cohort are summarized in Table I. The mean age of the patients was 7.3 years (range 2.6–17.2 years). The average interval from diagnosis at the time of study was 19.6 months. The average duration on maintenance was 12.4 months.

Methods

We utilized the Medication Event Monitoring System (MEMS; Aprex Corporation, Fremont, CA) pill containers to determine compliance. The use of these containers has been previously reported by us as well as other investigators [9–12]. Patients and their parents were not informed of the function of the MEMS pill container. 6-MP was dispensed in the MEMS container or parents were asked to transfer their pill supply to the container. The patients (or the parents) were instructed to take pills only from this container. Data from the MEMS were retrieved by a computer which provides a list of dates and times of all openings of the pill container. Patients were considered to have missed a dose if there was no recorded opening for the specific dose within the study period. Compliance was defined as the number of days doses were taken as a percentage of the total number of days doses were prescribed during the study period. To test the hypothesis that the better outcome described with evening administration [5] is due, in part, to lower compliance in the morning than with evening administration, a group of patients had evaluations of compliance with both morning and evening schedules of administration in a randomized fashion for 4–6 weeks each arm (variability depending on the next clinic visit). Their compliance over these two separate periods was averaged to determine their mean compliance. Patients were seen at least monthly in the outpatient clinic. The study protocol was approved by our Research Ethics Committee and all parents gave informed consent. Our Ethics Committee permitted us not to disclose that compliance was the end point of the study in order to prevent such knowledge from potentially changing it.

TABLE II. Compliance as Measured by the MEMS

Patient no.	Age (years)	Period from diagnosis (months)	Period on maintenance therapy (months)	Period of study (days)	Overall compliance[a] (%)
1	6	32.7	27.8	37	38
2	8.2	17.8	10.6	15	66.7
3	13.5	11.6	4.6	72	74.3
4	10.4	9.2	1.9	21	76.2
5	14.6	31.3	24.5	84	82.1
6	4.7	12.3	2.0	94	85.1
7	4.5	27.9	13.7	36	86.1
8	5.9	31.9	29.7	48	89.6
9	16.2	30.7	23.3	35	91.4
10	4.8	2.0	0	55	92.7
11	8	15.0	6.8	28	92.9
12	17.2	31.3	23.6	36	94.4
13	3.5	11.4	0.9	55	94.5
14	3	5.2	3.0	52	94.6
15	2.6	33.8	20.9	41	95
16	3.3	22.3	14.7	27	96.3
17	6.2	12.4	2.1	54	96.3
18	14.5	24.4	17.6	34	97.1
19	2.9	2.9	0.6	60	100
20	3.2	26.8	18.1	24	100
21	3	18.8	11.2	24	100
22	6	13.5	5.7	64	100
23	5.8	32.9	30.9	35	100
24	6.5	13.7	5.6	26	100

[a]Compliance = % of days medication event recorded of total days evaluated [mean = 89.4 ± 14.2% (±SD); median = 94.4%].

RESULTS

A summary of the results of our patient cohort is given in Table II. For the 24 patients evaluated the mean over-

all compliance was 89.4%, with a range of 38–100% and a median of 94.4%. Patients were evaluated for a mean of 44 days (range 15–94 days). Eight patients (33%) had less than 90% compliance, of which 4 (17%) had less than 80% compliance. We found no correlation between compliance and patient age and time on maintenance therapy. Within each patient there was very little variability in compliance overtime. Eight patients were evaluated for differences between compliance with a morning vs. an evening schedule (Table III). There was a trend toward improved compliance in the evening than in the morning. Five patients had an increase in compliance, one a decrease on an evening schedule, and two had 100% compliance on both schedules.

DISCUSSION

Our patients and their families were not informed of the function of the MEMS containers. One third of our patients had less than 90% compliance, therefore, on average these patients would miss a pill every 10 days. The appropriate level of compliance required to ''cure'' ALL, or conversely, the degree of non-compliance that results in relapse, is not known. In leukemia therapy one has to assume the goal is for as close as possible to 100% compliance. One group has suggested that children with leukemia should take at least 95% of their prescribed medication to be considered fully compliant [13]. We found that only 42% (Table II) of patients took 95% or more of their prescribed doses, and conversely, 33% of patients took less than 90%. It is possible, because of differences in the appearance of a MEMS container from a regular pill container, that its use was an intervention which would favor an increase in compliance and our finding may in fact be an overestimate of the true compliance of our patient group. There are several reports of compliance in ALL [4,7,8,14–17], but to the best of our knowledge, this is the first study to document the actual frequency of pill taking in childhood ALL.

Non-compliance with oral medications in hematological malignancies may have an adverse effect on patient survival [18]. In a prospective study of compliance in children with ALL in remission using 6-MP blood concentrations, one third of the patients studied had undetectable levels [7]. Measurement of 6-thioguanine nucleotides (6-TGNs) and methyl mercaptopurines (MeMPs) in children on UK (United Kingdom) ALL trials suggests that 10–20% of patients do not comply with their prescribed therapy [16]. Previous work has demonstrated that low systemic exposure to 6-MP, as reflected by area under the concentration vs. time curve, during maintenance therapy for ALL in childhood is associated with an increased likelihood of an adverse outcome [3]. Non-compliance would constitute an obvious cause of low systemic exposure. Although prospective studies directly relating poorer outcome in ALL to non-compliance are lacking, until data to the contrary are available, current data suggest that non-compliance in ALL may lead to an increased risk of relapse.

Other influences on systemic exposure may include physician non-compliance [19,20] and pharmacokinetic and pharmacogenetic variability [6,21,22]. Failure to prescribe protocol recommended doses of 6-MP and methotrexate was found to be associated with a higher relapse rate in ALL patients [20]. Clinically significant diurnal variation in 6-MP kinetics [23] and a reported case of a child with no detectable levels of 6-MP despite supervised administration [21] illustrate the wide kinetic variability possible with 6-MP. The relative importance of non-compliance compared to pharmacokinetic, pharmacogenetic, and pharmacodynamic factors in defining the risk of ALL relapse is not known. As such, the degree of compliance constituting optimum therapy is difficult to define. However, until such data are available, the aim for patients should be for as close to 100% compliance as possible during therapy for ALL.

Traditional methods for assessing compliance are patient self-reports, physician assessments, and pill counts. Patients and physicians generally overestimate compliance [24]. The phenomenon of ''pill dumping'' undermines the accuracy of pill counts [25]. Laboratory methods are often limited by availability of appropriate assays. The detection of drugs and their metabolites is generally not informative for the intervals between testing. Drug monitoring assays are more likely to indicate compliance just preceding testing rather than long-term compliance and therefore can be misleading and may reflect the ''white coat'' effect [26]. The accumulation of 6-TGNs), the intracellular cytotoxic metabolite of 6-MP, requires more continuous use and may be the optimal assay to monitor patient compliance [13]. Significant interindividual variation in erythrocyte 6-TGNs among patients receiving similar doses of 6-MP limits the usefulness of ''spot'' levels to assess compliance. Serial levels may be more valuable as intrapatient variation is less significant [27]. Optimal levels for erythrocyte 6-TGNs have yet to be defined. The results of prospective studies attempting to define the clinical correlation of these levels with outcome should be informative [13,27]. One also has to acknowledge the rare patient (approximately 1 in 300) with a genetic deficiency of thiopurine methyltransferase (TPMT) who presents with intolerance to the usual maintenance doses of 6-MP.

The MEMS is an electronic device used to assess compliance. A microprocessor chip in the cap allows the recording of the date and time of each opening of the pill container. This information can be retrieved and an account of these dates and times generated. Analysis of these data can provide estimates of compliance and the

TABLE III. Evaluation of Morning vs. Evening Schedules

Patient	Age (years)	Time from diagnosis (months)	Period on maintenance therapy (months)	% Compliance		Difference between AM vs. PM[a]
				AM schedule	PM schedule	
NA	6	13.5	5.7	100[b]	100	0
JC	6.2	12.4	2.1	96.2	96.4[b]	0.2
SB	4.8	2	0	89.3[b]	96.3	7
CD	2.9	2.9	0.6	100[b]	100	0
SS	4.7	12.3	2	83.3[b]	86.5	3.2
KM	13.5	11.6	4.6	48.7	100[b]	51.3
MM	3	5.2	3	96.2[b]	100	3.8
HN	3.5	11.4	0.9	96.4	92.6[b]	−3.8

[a]Wilcoxon signed rank test ($P = 0.12$).
[b]Schedule first evaluated for patient.

patient's ability to conform to dosing schedules. It provides objectivity to compliance assessments while circumventing the problems associated with laboratory methods. When no openings are recorded, one can be reasonably certain that no pills were taken. However, it is not a perfect method as the recording of an opening and closing of the pill bottle is only circumstantial evidence that a pill was taken. It is, however, conceivable to assume that patients who make the effort of opening and closing the container at the appropriate time each day are likely to be compliant.

Our study also found a trend toward improved compliance with an evening rather than a morning schedule of administration. Five of the eight patients who were monitored on both schedules had better compliance on the evening schedule. Although statistical significance was not achieved, likely because of our small sample size, this finding is of clinical relevance. Rivard et al. [5] found a better outcome for ALL patients taking 6-MP on an evening rather than a morning schedule during maintenance therapy. Factors accounting for this observation were not elucidated. However, diurnal variation in 6-MP kinetics has been demonstrated. Higher 6-MP levels were found with evening, in comparison, to morning administration [23] and could account for the finding of Rivard et al. [5]. Our data support the hypothesis that the timing of administration of 6-MP in children with ALL may be crucial in some patients (e.g., patient KM).

Koren et al. [3], in a group of low and standard risk ALL, compared the systemic exposure to 6-MP in patients with and without relapse. The mean total systemic exposure to 6-MP in patients who relapsed was 35% less than in patients who did not relapse. Hale and Lilleyman [28] reported an improvement in 5 year relapse-free survival in patients treated after 1980 compared to children treated before 1980 and related this to an increase of 22% in the median total dose of 6-MP prescribed. These data suggest that optimal systemic exposure to 6-MP is required for therapeutic efficacy. Patients who are noncompliant will compromise their exposure to the drug and increase their risk of relapse. If these patients can be identified early enough, measures can be taken to optimize their care. The measurement of intracellular red blood cell (RBC) 6-MP metabolites has been advocated as a method to identify these patients [13,16]. 6-MP has little cytotoxic activity by itself, but the native drug is converted to its 6-TGNs, which are then incorporated into DNA and induce cytotoxicity. Intracellular 6-TGNs can be converted into inactive MeMPs by TPMT.

Low levels of both 6-TGNs and MeMPs would be suggestive of non-compliance, however, they would not be conclusive of this. Pharmacokinetic factors including poor or no oral absorption can also account for low levels. For patients with poor oral bioavailability, measures to improve compliance would be inappropriate, but more significantly, an erroneous conclusion of non-compliance can potentially lead to disruptive relationships between patients, their families, and caregivers. Conversely, for patients who are truly non-compliant, increasing drug doses to overcome pharmacokinetic and/or pharmacodynamic variability may expose them to undue risk if they were then to start taking their pills.

It is clear that no single method is ideal for determining and monitoring maintenance therapy. Ideally, determination of both compliance with pill taking and pharmacokinetic studies should be complementary to RBC metabolite assays. It has been suggested for protocols where 6-MP is largely relied upon for maintenance therapy that there is a need to identify patients with high risk pharmacokinetic profiles [13]. A prospective cohort study in children with ALL utilizing pill counts, medication event monitoring, and red cell 6-MP metabolite assays as well as their correlation to white cell counts, and risks of relapse may be useful to clarify the role of each of these methods in the clinic setting. In the interim, it is likely that a proportion of pediatric ALL patients may be receiving inadequate maintenance therapy because of non-compliance and/or pharmacokinetic or pharmacogenetic variation. Until more data are available, an algorithmic approach is proposed (Fig. 1) which is

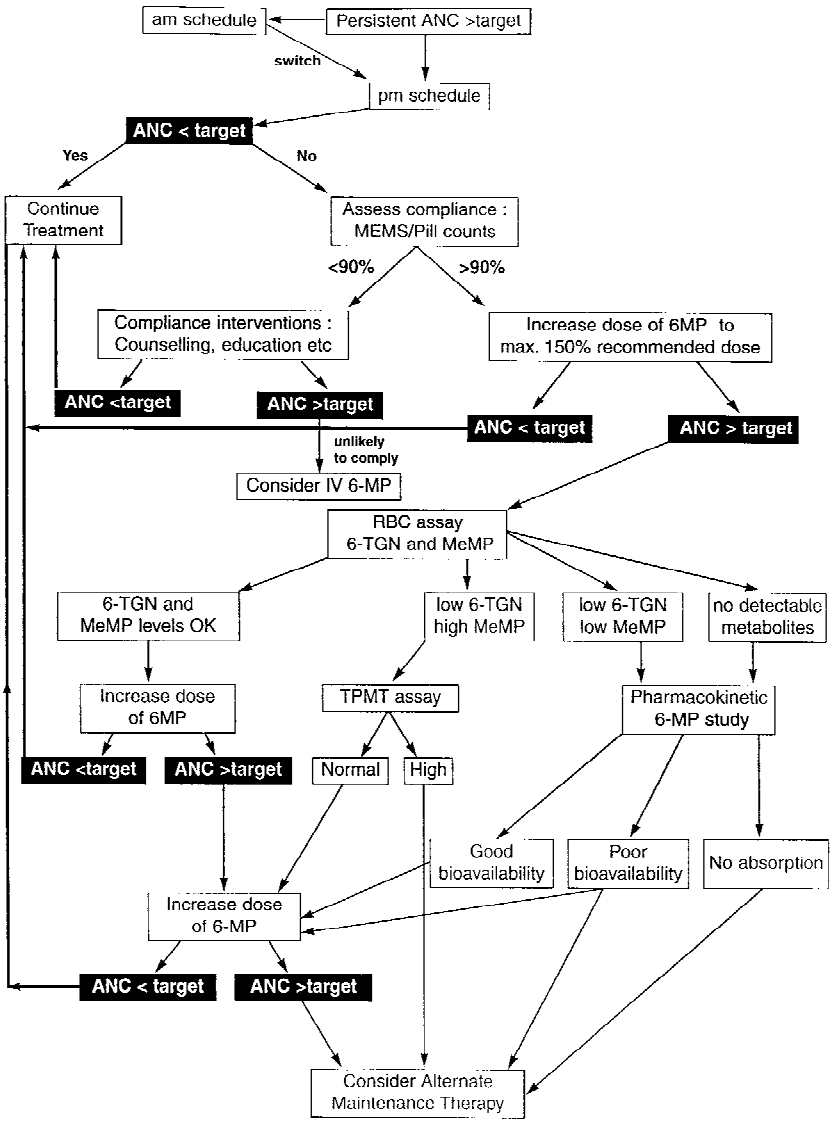

Fig. 1. Algorithm for monitoring maintenance therapy. ANC, absolute neutrophil count; IV, intravenous.

based on the current traditional practice to adjust doses of maintenance drugs to keep patient white cell counts in a target range. The findings that lower 6-TGN levels are associated with an increased risk of relapse [29] and higher 6-TGN levels are associated with greater myelosuppression [27] would tend to support utilizing white blood cell counts to guide dosage changes during maintenance therapy. This algorithm should identify patients who potentially are at risk of suboptimal maintenance therapy.

The relatively poor and highly variable oral availability of 6-MP, the need for long-term daily administration, and the critical need for compliance all suggest the need for assessment of new dosage forms.

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